UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/087,513 | 05/29/98 | KANEKO | Y 0010-0929-0X |

022850 HM12/0705
OBLON SPIVAK MCCLELLAND MAIER & NEUSTADT
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON VA 22202

| EXAMINER | |
|---|---|
| WILSON,M | |
| ART UNIT | PAPER NUMBER |
| 1633 | 12 |

DATE MAILED: 07/05/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/087,513 | KANEKO ET AL. | |
| | Examiner | Art Unit | |
| | Michael Wilson | 1633 | |

*-- The MAILING DATE of this communication appears on the cover she t with the correspond nce address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 April 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *14,15,19 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,15,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

## DETAILED ACTION

Applicant's arguments filed 4-11-01, paper number 11, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1-13 and 16-18 have been canceled. On page 10, line 3, of applicants response, applicants state that claim 20 is canceled. However, claim 20 is not canceled on page 3, line 2, or anywhere else in applicants response. Therefore, claims 14, 15, 19 and 20 are pending and under consideration in the instant application.

### *Claim Rejections - 35 USC § 112*

1. The amendment filed 4-11-01 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: page 26, line 17, does not necessarily refer to Wyatt et al. because Wyatt refers to a Δ297-329 mutant with a deletion spanning the V3 loop and insertion of 3 amino acids in its place while the specification merely teaches the vv-ΔV3 mutant with the Δ297-329 deletion. Wyatt does not teach the deletion spanning the V3 loop was nucleotides 297-329. Wyatt uses the HXBc2 strain of HIV and not HIV-IIIB as in the instant invention (page 26, line 12). It cannot be determined that reference 15 as on page 26, line 17, is Wyatt et al. as newly amended, that Wyatt taught deleting nucleotides 297-329 of HIV-IIIB or how the structure of the Δ297-329 mutant of Wyatt is the same as the structure of the vv-ΔV3 mutant disclosed on page

26, line 16. Page 35, lines 10 and 11, does not support that page 26, line 12, refers to Wyatt. Applicant is required to cancel the new matter in the reply to this Office action.

2. Claims 14, 15, 19 and 20 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is drawn to a method of making a vaccine against HIV and a vaccine against HIV. The specification identifies the essential feature of the invention is an HIV envelope glycoprotein with a deletion in the V3 loop which was known in the art.

The specification discusses HIV-IIIB mutants with the ▵297-329 deletion (page 26, line 26) and refers to Wyatt (1992, J. Virol., Vol. 66, 6997-7004). Wyatt refers to a Δ297-329 mutant of the HXBc2 strain of HIV with a deletion spanning the V3 loop and insertion of 3 amino acids in its place while the specification merely teaches the vv-ΔV3 mutant has a Δ297-329 deletion. Wyatt does not teach the deletion spanning the V3 loop was nucleotides 297-329, and Wyatt uses the HXBc2 strain of HIV and not HIV-IIIB as in the instant invention (page 26, line 12). Therefore, it cannot be determined what applicants consider nucleotides 297-329 of HIV-IIIB or how the structure of the Δ297-329 mutant of Wyatt correlates to the structure of the vv-ΔV3 mutant disclosed on page 26, line 16. It cannot be determined from the specification whether the vv-ΔV3 (page 26, line 16) has a deletion of 297-329 and Gly-Ala-Gly inserted in

place of the loop or merely a deletion of nucleotides 297-329. Overall, the structure of vv-ΔV3 cannot be determined.

The specification discloses the 1ΔV3, 7ΔV3 and 8ΔV3 mutants (e.g. Example 14, page 34, Fig. 1) but does not teach how to make such mutants, how the mutants differ from each other, how the mutants differ from the vv-ΔV3 mutant with the Δ297-329 deletion (page 26) or the structural elements of the mutants. The specification discloses the WTP-2, WTP-5 and WTP-8 (page 35, line 3; page 36, line 16; Fig. 1), but it is unclear how the envelope gene in these vectors differs from each other or from the V3 mutants or whether these vectors are considered "modified". The specification does not disclose using these vectors or any cells expressing envelope glycoproteins containing modified immunodominant epitopes to induce a cellular immune response in a patient. The specification does not teach the cellular immune response is directed toward HIV or that such an effect is therapeutic or prophylactic. The specification does not teach how to modify the envelope glycoprotein of any strain of HIV other than HIV-IIIB. Therefore, the specification does not provide adequate written description regarding the structure of any envelope glycoprotein of HIV with a deletion in V3 that is essential to induce cellular immunity or to obtain a therapeutic or prophylactic effect.

3. Claims 14, 15, 19 and 20 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The disclosed purpose of the instant invention is to provide therapy for patients with HIV (page 1, line 12). Therefore, the field of the claimed invention is a vaccine for inducing cellular immunity to treat HIV infection and a method of making such a vaccine. While the art teaches the steps required to induce a cellular immune response against the envelope glycoprotein of HIV, the art does not teach such cellular immune responses are therapeutic against HIV or the level or specificity of a cellular immune response that is therapeutic against HIV. Therefore, the following enablement rejection is based on using the vaccine claimed to induce a therapeutic cellular immune response against a conserved epitope of HIV envelope glycoprotein.

Claims 14 and 15 are directed toward making a vaccine comprising a nucleic acid encoding an HIV envelope glycoprotein with a deletion of V3. Claims 19 and 20 are directed toward a vaccine comprising cells expressing an HIV envelope glycoprotein with a deletion of V3.

At the time of filing, it was unpredictable whether a nucleic acid construct would have a therapeutic or prophylactic effect against HIV. Ross of record (September 1996, Human Gene Therapy, Vol. 7, pages 1781-1790) states a major technical impediment to gene transfer is the lack of ideal gene delivery systems including vectors, promoters and modes of delivery (page 1782, column 2, first full paragraph). These technical parameters are required to obtain efficient delivery and sustained expression of the gene (Verma of record, Sept. 18, 1997, Nature, Vol. 389, page 239-242; see page 239, 3rd column, line 10). The difficulties in sustaining expression of a gene cause an unpredictability in obtaining a therapeutic or prophylactic effect in a patient (Ross,

page 1789, column 1, first paragraph). Therefore, the parameters required to obtain a therapeutic effect using DNA were unpredictable at the time of filing.

Regarding vaccines, it was unpredictable how to obtain a therapeutic effect against a virus using a single antigenic stimulus as a vaccine. Haynes of record (1993, Science, Vol. 260, pages 1279-1286) teaches the classic approach to vaccine development involves exposing cells of the immune system to the proper antigenic stimulus which stimulates a beneficial immune response. The prior art presents few examples where a single antigenic stimulus, such as a small limited peptide or a whole protein is found to engender a therapeutic or protective immune response. The successful art-recognized immunogens used as vaccines are derived from whole killed or live attenuated pathogens, comprised of complex antigenic mixtures or comprised of inactivated toxins. Many of these successes were achieved with a certain degree of luck, influenced by some particular peculiarity or aspect of a given pathogenic agent. Therefore, it was unpredictable how to obtain a therapeutic effect against a virus using a single antigen.

Specifically regarding HIV vaccines, Stricker of record (Medical Hypotheses, June 1997, Vol. 48, pages 527-9; see page 527, last paragraph through all of page 528) teaches that attempts to develop a vaccine against HIV have been unsuccessful. In fact, HIV infection has defied the creation of an effective vaccine or immunotherapeutic. Overall, a lack of understanding about cellular immunity against HIV, the sequence variability of HIV and the rapid replication of HIV, as disclosed by Bangham of record contribute the ineffectiveness of vaccines against HIV (Nov. 29, 1997, Lancet, Vol. 350, pages 1617-1621; page 1617, top of column 1). It is not known

what renders an antigen capable of stimulating beneficial or protective CTL responses to HIV. Therefore, the art at the time of filing did not teach that the envelope glycoprotein of HIV could be used to induce a therapeutic cellular immune response against HIV. Thus, the parameters required to obtain a therapeutic cellular immune response against HIV was unpredictable at the time of filing.

The specification discloses the vv-ΔV3 mutant which has a Δ297-329 deletion (page 26, line 17) and refers to Wyatt (1992, J. Virol., Vol. 66, 6997-7004). Wyatt refers to a Δ297-329 mutant of the HXBc2 strain of HIV with a deletion spanning the V3 loop and insertion of 3 amino acids in its place while the specification merely teaches the vv-ΔV3 mutant has a Δ297-329 deletion. Wyatt does not teach the deletion spanning the V3 loop was nucleotides 297-329, and Wyatt uses the HXBc2 strain of HIV and not HIV-IIIB as in the instant invention (page 26, line 12). Therefore, it cannot be determined what applicants consider nucleotides 297-329 of HIV-IIIB or how the structure of the Δ297-329 mutant of Wyatt correlates to the structure of the vv-ΔV3 mutant disclosed on page 26, line 16. It cannot be determined from the specification whether the vv-ΔV3 (page 26, line 16) has a deletion of 297-329 and Gly-Ala-Gly inserted in place of the loop or merely a deletion of nucleotides 297-329. Overall, the structure of vv-ΔV3 cannot be determined.

The specification discloses the 1ΔV3, 7ΔV3 and 8ΔV3 mutants (e.g. Example 14, page 34, Fig. 1) but does not teach how to make such mutants, how the mutants differ from each other, how the mutants differ from the vv-ΔV3 mutant with the Δ297-329 deletion (page 26) or the

structural elements of the mutants. The specification also discloses the WTP-2, WTP-5 and WTP-8 (page 35, line 3; page 36, line 16; Fig. 1), but it is unclear how the envelope gene in these vectors differs from each other or from the V3 mutants or whether these vectors are considered "modified".

Overall, the specification does not provide adequate guidance for one of skill to make the vectors disclosed, how the vectors differ from each other or the structural elements of the vectors by teaching how to make the Δ297-329 mutant of HIV-IIIB.

The specification provides CTL and antibody-dependent cell-mediated cytotoxicity data *in vitro* (page 35-38), but does not provide any examples of inducing cellular immunity against HIV *in vivo*. Nor does the specification provide adequate correlative evidence between *in vitro* data and *in vivo* results such that a therapeutic cellular immune response against HIV could be obtained *in vivo*.

The state of the art at the time of filing was that CTL assays *in vitro* produce variable results depending on the target cells used, the effector to target ratio used, and the incubation time (Lancki of record, 1992, Biotherapy, Vol. 5, pages 71-81; see page 72, column 1, line 1) CTL assays combine PBL and target cells that are artificially "loaded" with antigen. The amount of antigen required on the target cell surface to induce a CTL response depends upon the immunostimulatory epitope of the antigen, the type of immune response and the strength of the immune response desired. Moreover, CTL assays do not account for the complex interaction of the immune response and cytokine regulation that occurs *in vivo*. For example, Bachmann of

record reviews the use of the cellular immune response both *in vivo* and *in vitro* in viral assay systems (1994, Current Op. Immunol. Vol. 6, pages 320-326). A comparison of sensitivities shows that radioactive CTL assays are more sensitive than *in vivo* assays, but that results of secondary *in vitro* stimulation need to be verified by *in vivo* assay. On page 323, Bachmann states one should be very cautious not to 'over-interpret' results obtained by a cytolytic assay where cells are stimulated *in vitro* because the results may be biologically irrelevant without *in vivo* confirmation. Therefore, it was unpredictable at the time of filing whether a CTL response obtained *in vitro* could be obtained *in vivo* or that a cellular immune response obtained *in vivo* equivalent to the cellular immune response obtained *in vitro* will have any biological relevance.

The *in vitro* CTL and ADCC assays disclosed in the instant application require PBMC isolated from an HIV patient and autologous B-LCL or Jurkat cells transfected with the vectors of the invention as target cells which do not correlate to cells or nucleic acids used to treat viral infection *in vivo*. The specification does not teach the strain of HIV in the patients used to make the PBMC *in vitro*, the level of antigen expression on the surface of target cells *in vitro*, the level of expression required *in vivo*, or how the immune response obtained *in vitro* correlates to response expected *in vivo*. It is not clear that the ratios of target to effector ratio used *in vitro* correlates to the ratio of transfected cells to effector cells that would occur *in vivo*. It addition, applicants activated the PBMC with antibodies which is an artificial means used to increase the activity of the cytotoxic cells and does not correlate to conditions found in the HIV patients because patients PBMCs are not stimulated with anti-CD3 antibodies. In addition, the

specification does not teach that the level of cellular immunity *in vitro* would have any therapeutic benefit in a patient. Given the state of the art regarding the lack of correlation between *in vitro* and *in vivo* cytotoxicity taken with the guidance provided in the specification, it would have required one of skill undue experimentation to determine the parameters required to obtain an cellular immune response *in vivo* that has a therapeutic or prophylactic effect.

Applicants argue that *in vitro* CTL data correlates with *in vivo* protective efficacy as supported by Johnson, Daniel and Wyand. Applicants argument is not persuasive because Johnson, Daniel and Wyand do not compare the CTL response *in vitro* with the CTL response obtained *in vivo*. While a CTL response was obtained *in vivo*, the teachings of Johnson, Daniel and Wyand do not correlate to the claimed invention because HIV and SHIV are different, and because the SHIV used by Johnson, Daniel and Wyand have different structural elements than the vector of the instant invention (deletions in nef, vpr and U3).

Claims 14, 15, 19 and 20 encompass modifying the envelope glycoprotein of any strain of HIV. The state of the art at the time of filing was such that the V3 region of HIV varied between HIV strains and mutated frequently (page 1, line 15; page 2, line 13; page 3, line 3). The specification only teaches modifying the V3 loop of the HIV-IIIB envelope glycoprotein (page 26, line 12). The specification does not teach how to modify the V3 loop of the envelope glycoprotein of any other strain of HIV or correlate the V3 loop of HIV-IIIB to other strains of HIV such that similar modifications could be made or that a therapeutic cellular immune response could be induced against the glycoprotein.

Applicants demonstrate different modifications of HIV-IIIB cause different effects (e.g. 1$\Delta$V3, 7$\Delta$V3 or 8$\Delta$V3 mutants induce different immune responses, Fig. 1). Therefore, the specification does not enable one of skill to determine how to modify the V3 loop of any HIV envelope glycoprotein such that a therapeutic cellular immune response against HIV is obtained.

Overall, the specification does not provide adequate guidance regarding how to induce a therapeutic cellular immune response against HIV *in vivo*. Given the state of the art taken with the guidance provided in the specification, it would require one of skill undue experimentation to use any nucleic acids as claimed to induce a therapeutic cellular immune response against HIV *in vivo*.

Claims 14 and 15 appear to be free of the prior art of record because the prior art of record did not enable combining a nucleic acid encoding an HIV envelope glycoprotein with a deletion of the third variable loop as claimed with an adjuvant such that a vaccine is made. Claims 19 and 20 appear to be free of the prior art of record because the prior art of record did not teach or suggest combining cells expressing an HIV envelope glycoprotein with a deletion in the third variable loop with an adjuvant.

***Conclusion***

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

DEBORAH J. R. CLARK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600